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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	9

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/585,077	SUMMAR ET AL.	
	Examiner	Art Unit	
	Diana Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2000 and 27 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. The instant application is a continuation-in-part of U.S. Application No. 09/323,472, filed June 1, 1999, now U.S. Patent No. 6,346,382. The specification should be amended to provide the status of the '472 application.

Specification

2. The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a) and (a)(2). However, the specification fails to comply with one or more of the requirements of 37 CFR § 1.821 through 1.825 because the specification recites sequences that lack description by the appropriate sequence identifier set forth in the "Sequence Listing" as required by 37 CFR § 1.821(d). See, for example, p. 83. Appropriate corrections for compliance are required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-12 and 15-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods in which susceptibility to "sub-optimal urea cycle function" and/or susceptibility to bone marrow transplant toxicity are determined in a human subject by detecting the presence of a threonine at amino acid 1405 of CPSI and by detecting a nucleotide sequence encoding that threonine in

the CPSI gene, does not reasonably provide enablement for methods in which susceptibility to "sub-optimal urea cycle function" and/or susceptibility to bone marrow transplant toxicity in any type of "subject" are determined by detecting the presence of any polymorphism in the CPSI gene, including any C to A transversion in exon 36 of the CPSI gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods of treating or preventing "sub-optimal urea cycle function" in a subject (claims 1-12) and methods of treating or preventing bone marrow transplant toxicity in a subject (claims 15-23) that may comprise a step in which a polymorphism of the CPSI gene is detected in the subject. This rejection applies to the claims to the extent that they encompass methods in which CPSI gene polymorphisms other than polymorphisms resulting in the presence of a threonine at amino acid 1405 of the CPSI polypeptide are detected as an indicator of "sub-optimal urea cycle function" or susceptibility to bone marrow transplant toxicity.

The specification discloses that the presence of a threonine at amino acid 1405 of CPSI is indicative of susceptibility to "sub-optimal urea cycle function" and bone marrow transplant toxicity (see, e.g., Example 1). In view of the teachings of the specification, it is thus clearly within the ability of one of skill in the art to detect the presence of threonine at amino acid 1405 of CPSI and/or a nucleotide sequence encoding this threonine in the CPSI gene as an indicator of susceptibility to "sub-optimal urea cycle function" and/or bone marrow transplant toxicity. However, it is

unpredictable as to whether one of skill in the art could practice the invention in a manner reasonably commensurate with the present claims. The instant claims are not limited to methods in which the presence of the T1405 allele is detected, but rather are sufficiently broad so as to encompass detection of any CPSI polymorphism as an indicator of disease susceptibility, or, in the case of dependent claims 12 and 23, detection of any C to A transversion in CPSI exon 36 as an indicator of such susceptibility. As the specification provides no evidence of C to A polymorphisms within exon 36 or elsewhere in the CPSI gene that are actually associated with either CPSI deficiency or susceptibility to bone marrow transplant toxicity, it is unpredictable based on the teachings of the specification as to whether there are any other C to A polymorphisms that occur in CPSI, and particularly, as to whether there are any such polymorphisms that are actually associated with susceptibility to the conditions set forth in the instant claims. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention. The prior art as exemplified by Hoshide et al (J. Clin. Invest. 91(5):1884-7 [5/1993]) discloses a G to C polymorphism at the 3' end of an exon of the CPSI gene that is associated with CPSI deficiency (see entire reference, especially p. 1885). Similarly, Finckh et al (Human Mutation 12:206-211 [8/1998]) teach a C to T polymorphism that results in a Thr544Met substitution in CPSI, which substitution is associated with CPSI deficiency. Accordingly, one of skill in the art could clearly detect these known, disease-associated polymorphisms as indicators of susceptibility to CPSI deficiency. However, the existence of a few particular disease associated

polymorphisms in a gene is insufficient to suggest that any polymorphism found in that gene will be disease related. Further, Finckh et al cite examples of a number of polymorphisms found in different variants of the human CPSI gene (Table 2) that do not appear to be disease associated, stating that "In addition to the disease-linked mutation, sequencing data from the parents and healthy controls revealed a great number of nucleotide differences" with respect to the originally reported CPSI sequence (p. 209; see also p. 210). Additionally, it is well known to those of skill in the art that many single base transitions in genes constitute polymorphisms that have no effect on the expression or function of the polypeptide encoded by that gene (e.g., silent mutations). No quantity of experimentation would be sufficient to allow one of skill in the art to detect these types of transitions as indicators of the disorders set forth in the claims, as no such relationship exists. Further, the few, disorder-associated polymorphisms described in the specification and in the art are clearly not representative of the broad genus of polymorphisms encompassed by the claims, particularly as Finckh et al demonstrate that there are polymorphisms found in the CPSI genes of healthy individuals that are unrelated to disease. Thus, in view of the guidance and teachings provided by the specification and the art, it is unpredictable as to whether one of skill in the art could practice the instant invention in a manner reasonably commensurate with the claims, and the quantity of experimentation that would be required to practice the invention as claimed is clearly undue. Furthermore, it is noted that the teachings of the specification and of the prior art enable one of skill in the art to detect particular CPSI polymorphisms as indicative of disease in human subjects. However, neither the

specification nor the art provide evidence of disease-associated polymorphisms in other types of "subjects", or disclose that there is, e.g., a 1:1 correspondence between polymorphisms found in the CPSI gene of humans and other non-human "subjects", such that a skilled artisan would conclude that one could predictably extrapolate findings of polymorphism-associated disease in humans to other types of subjects. Thus, while teachings of the specification and of the prior art would allow one of skill in the art to practice methods of treating a human subject comprising steps of determining susceptibility to "sub-optimal urea cycle function" and/or susceptibility to bone marrow transplant toxicity by detecting the presence of a threonine at amino acid 1405 of CPSI and by detecting a nucleotide sequence encoding that threonine in the CPSI gene, it would require undue experimentation to use the methods of the instant invention in a manner reasonably commensurate with the claims.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-14 and 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-14 are indefinite over the recitation of the limitation "subject in need thereof." It is unclear as to what subjects would be encompassed by this language, and thereby encompassed by the claims. For example, how would one distinguish an individual in need of a "therapeutically effective amount of a nitric oxide precursor" from an individual not "in need?" Clarification is required.

Claims 11-14 and 22-25 are indefinite because it is unclear as to how the further step of "initially detecting a polymorphism" relates to treating or preventing sub-optimal urea cycle function as in claim 1 or to treating or preventing bone marrow transplant disease as in claim 15. For example, how does the detecting of or failure to detect a polymorphism relate to or influence the method of treating/preventing?

Claims 12-14 and 23-25 are indefinite over the recitation of the limitation 'the polymorphism of the carbamyl phosphate synthetase polypeptide." There is insufficient antecedent basis for this limitation in the claims.

Claims 13-14 and 23-24 are indefinite over the recitation of the language "cDNA that corresponds to the CPSI gene." It is unclear as to what relationships between cDNA and gene would be encompassed by the term "corresponds." Accordingly, the metes and bounds of the claims are unclear.

Claims 14 and 25 are indefinite because it is unclear as to whether the claims are intended to refer to a "C to A transversion" or an A to C transversion. Claims 14 and 25 subsequently recite "a change in the triplet code from AAC to ACC" (which requires an A to C transversion rather than the recited C to A transversion). Further, the codon ACC encodes threonine (as recited in the claims), whereas AAC encodes asparagine. Clarification is required. It is further noted that claims12-13 and 23-24 also refer to a "C to A transversion").

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 6, and 10 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Mizutani et al (Tohuku L. Exp. Med. 142:15-24 [1984]).

Mizutani et al disclose the treatment of hyperammonemia in humans with arginine and citrulline (see entire reference, especially pages 17-18). Mizutani et al disclose that treatment with arginine or citrulline was found to prevent hyperammonemia (see entire reference, especially pages 19-20). Accordingly, Mizutani et al clearly anticipate the instant claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizutani et al (Tohuku L. Exp. Med. 142:15-24 [1984]).

Mizutani et al disclose the treatment of hyperammonemia in humans with arginine and citrulline (see entire reference, especially pages 17-18). Mizutani et al disclose that treatment with arginine or citrulline was found to prevent hyperammonemia (see entire reference, especially pages 19-20). The doses disclosed by Mizutani et al are an oral supplement of 8.0 g of L-citrulline daily in a 14 year old boy and an oral supplement of 5.0 g of L-arginine daily in a 7 year old boy (p. 20). Mizutani et al do not disclose the administration of the dosages of L-arginine or L-citrulline required by the instant claims. However, Mizutani et al disclose that of the two siblings studied, one responded better to L-arginine therapy, while the other responded better to L-citrulline therapy (see, p. 19-20, p. 22). Further, Mizutani et al disclose that dosages employed are determined by patient body weight (see, e.g., p. 17-18) and vary depending on the manner of administration (e.g., oral vs. intravenous; see p. 17-18). In view of the teachings of Mizutani et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Mizutani et al so as to have employed lower doses of arginine and/or citrulline meeting the requirements of the instant claims. It is noted that the claims are not limited to a particular dosage and method of administration disclosed in the specification as producing unexpected results. Given Mizutani et al's teachings regarding the varied response to arginine and citrulline in different patients, one of ordinary skill would have been motivated to have optimized dosages employed in different patients, and thereby

to have employed lower dosages meeting the requirements of the claims when appropriate for a particular patient. Further, given Mizutani et al's teachings, one of ordinary skill would have been motivated to have employed smaller doses meeting the requirements of the claims in smaller patients (e.g., infants), for the advantage of providing patients of lower body weight with a dose of the correct concentration, which concentrations are disclosed by Mizutani et al at, e.g., p. 17-18. Finally, a skilled artisan would have been further motivated to have employed lower doses when administering arginine and/or citrulline intravenously, as Mizutani et al exemplify the use of intravenous concentrations lower than the oral concentrations employed (see, e.g., p. 17). Thus, Mizutani et al suggest the claimed invention.

12. Claims 4-5, 15-19, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizutani et al in view of Davies et al (Bone Marrow Transplantation 17:1119-1125 [6/1996]).

Mizutani et al disclose the treatment of hyperammonemia in humans with arginine and citrulline (see entire reference, especially pages 17-18). Mizutani et al disclose that treatment with arginine or citrulline was found to prevent hyperammonemia (see entire reference, especially pages 19-20). However, Mizutani et al do not disclose the treatment or prevention of "bone marrow transplant toxicity" in a subject undergoing a bone marrow transplant, as set forth in the instant claims. Davies et al disclose that hyperammonemia is a complication of bone marrow transplantation (see entire reference, especially p. 1119). In view of the teachings of Davies et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was

made to have modified the treatment of Mizutani et al so as to have administered an arginine and/or citrulline treatment to a bone marrow transplant patient. As Mizutani et al disclose that arginine and/or citrulline treatment is effective in alleviating hyperammonemia, an ordinary artisan would have been motivated to have made such a modification for the advantage of preventing or alleviating hyperammonemia in the patient.

With respect to the doses required by claims 17-19, it is noted that the doses disclosed by Mizutani et al are an oral supplement of 8.0 g of L-citrulline daily in a 14 year old boy and an oral supplement of 5.0 g of L-arginine daily in a 7 year old boy (p. 20). Mizutani et al do not disclose the administration of the dosages of L-arginine or L-citrulline required by the instant claims. However, Mizutani et al disclose that of the two siblings studied, one responded better to L-arginine therapy, while the other responded better to L-citrulline therapy (see, p. 19-20, p. 22). Further, Mizutani et al disclose that dosages employed are determined by patient body weight (see, e.g., p. 17-18) and vary depending on the manner of administration (e.g., oral vs. intravenous; see p. 17-18). In view of the teachings of Mizutani et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Mizutani et al in view of Davies et al so as to have employed lower doses of arginine and/or citrulline meeting the requirements of the instant claims. It is noted that the claims are not limited to a particular dosage and method of administration disclosed in the specification as producing unexpected results. Given Mizutani et al's teachings regarding the varied response to arginine and citrulline in different patients, one of

ordinary skill would have been motivated to have optimized dosages employed in different patients, and thereby to have employed lower dosages meeting the requirements of the claims when appropriate for a particular patient. Further, given Mizutani et al's teachings, one of ordinary skill would have been motivated to have employed smaller doses meeting the requirements of the claims in smaller patients (e.g., infants), for the advantage of providing patients of lower body weight with a dose of the correct concentration, which concentrations are disclosed by Mizutani et al at, e.g., p. 17-18. Finally, a skilled artisan would have been further motivated to have employed lower doses when administering arginine and/or citrulline intravenously, as Mizutani et al exemplify the use of intravenous concentrations lower than the oral concentrations employed (see, e.g., p. 17). Thus, the combined teachings Mizutani et al and Davies et al suggest the claimed invention.

13. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mizutani et al in view of Davies et al as applied to claims 4-5, 15-19, and 21, above, and further in view of Vassal et al (Cancer, Chemotherapy and Pharmacology 37:247-253 (1996).

The combined references of Mizutani et al and Davies et al do not disclose administering arginine and/or citrulline to a patient suffering from hepatic veno occlusive disease (HVOD). Vassal et al disclose that HVOD, like hyperammonemia, is a complication of bone marrow transplantation (see entire reference, especially p. 247). In view of the teachings of Vassal et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Mizutani et al and Davies et al so as to have treated bone marrow transplant patients

suffering from HVOD by administering arginine and/or citrulline. The teachings of Mizutani et al in view of Davies et al suggest that treatment with arginine and/or citrulline will alleviate and/or prevent hyperammonemia in bone marrow patients, as set forth in paragraph 12, above. Accordingly, an ordinary artisan would have been motivated to have made such a modification for the advantage of preventing or alleviating hyperammonemia in bone marrow transplant patients suffering from HVOD.

Drawings

14. The formal drawings have been approved by the draftsperson.

Conclusion

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Levere et al (U.S. Patent No. 5,217,997 [6/1993]) disclose the administration of about 1 to 1500 mg per day of L-arginine to humans for the treatment of a variety of conditions, including hypertension (see entire reference, especially, e.g., col 6, lines 15-22).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
June 26, 2002

W. Gary Jones
Supervisory Patent Examiner
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